Science Should Be in the Public Domain

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ABSTRACT Variants of avian influenza H5N1 virus that are transmitted by the airborne route among ferrets have been identified. The National Science Advisory Board for Biosecurity has advised against publication of the details of the methods used to obtain these viruses and the amino acid changes that lead to transmission in ferrets. This decision is not based on sound scientific principles and risks setting a precedent that will make it easier to put in place highly restrictive regulations on scientific research and publication.

Two laboratories recently identified variants of an avian influenza H5N1 virus strain that are transmitted by the airborne route among ferrets (1). When these laboratories submitted their work for publication, the National Science Advisory Board for Biosecurity (NSABB) asked the authors to remove critical details from the manuscripts to ensure that they cannot be used by bioterrorists. This decision is wrong, not only because it rests on weak scientific grounds but also because it threatens to transform the landscape of biological research by setting a precedent to restrict research that can benefit, not harm, humanity.

The goal of the experiments was to determine what makes the influenza H5N1 virus transmissible. This virus strain is lethal in birds, humans, and ferrets, but airborne transmission does not readily occur among humans or ferrets. One group found that after 10 serial ferret-to-ferret passages, a virus that could spread by the aerial route among ferrets was obtained. The NSABB asked that details on how the virus was isolated and the amino acid changes leading to transmissibility be redacted from the manuscript.

A major reason why the NSABB does not want this information made public is that the virus is believed to be highly lethal in humans. The chair of the NSABB notes that he "can't think of another pathogenic organism that is as scary as this one." The reason for this view is exemplified by a recent statement about H5N1 in the *New York Times*: "In its natural form, it is known to have infected only about 600 people since its discovery in 1997, but it killed more than half of them" (2). We cannot say with any certainty that the virus has infected only about 600 people. What we do know is that among the 600 seriously ill individuals infected with H5N1 influenza virus who are admitted to the hospital, over half of them die.

The fatality rate of avian H5N1 influenza virus in humans is determined by dividing the number of fatalities by the number of infections. We do not know the last number—but there are hints that it could be quite large. In a recent study of rural Thai villagers, sera from 800 individuals were collected and analyzed for antibodies against several avian influenza viruses, including H5N1, by hemagglutination inhibition and neutralization assays (3). The results indicate that 73 participants (9.1%) have antibodies against one of two different H5N1 strains, suggesting that subclinical avian influenza virus infections are frequent in Thailand. If 9% of the rural Asian population has been infected with avian H5N1 influenza virus strains, it would dramatically change our view of the pathogenicity of the virus. Extensive serological studies must be done to determine the extent of human infection with avian H5N1 influenza viruses.

Ferrets are not humans and cannot be used to determine whether any influenza virus is a threat to humanity. Ferrets are a good model for influenza—they display similar flu-like symptoms, immune responses, and pathological alterations, such as elevated temperature, weight loss, and histological changes (4). It would be foolish to conclude that ferret influenza is the same as human influenza in all aspects. Not all influenza virus strains have the same virulence in humans and ferrets. An example is the 2009 pandemic H1N1 virus, which caused severe infections in some ferret studies, but was relatively mild in humans (5). The fact that an H5N1 virus is transmissible among ferrets does not mean that it will be equally transmissible among humans. The experiment to answer this question cannot be done.

Passage of viruses in a different host is one strategy for reducing viral virulence in humans. Many live, attenuated viral vaccines have been produced in this way, including vaccines against yellow fever virus and poliovirus (6, 7). The possibility that passage of the H5N1 virus in ferrets will attenuate its virulence in humans has been ignored.

It is highly unlikely that the sequence of the ferret-adapted H5N1 influenza virus would be used for bioterrorism, as its potential for transmission and lethality in humans is unknown. Bioterrorists do not want to carry out an experiment; they want to instill terror. Assuming that the H5N1 virus passaged in ferrets could start a pandemic, knowing the amino acid changes required for transmission in ferrets does not immediately enable construction of a biological weapon. The virus must be recovered from cloned DNA, which requires finely honed skills in virology. A good virologist would have already thought to serially passage the H5N1 virus in ferrets, which would be faster than reconstructing a virus from the nucleotide sequence.

It seems simplistic to assume that laboratory-modified viruses can cause extensive disease in humans. When humans genetically modify viruses, they generally do not know what the virus needs to replicate efficiently, cause disease, and transmit among humans. Consequently, they are likely to introduce changes that attenuate pathogenesis in humans. In nature there is strong selection for fitness and transmission. To think that we can duplicate the enor-

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mous diversity and selection pressures that occur in the wild is a severe case of scientific hubris.

No one can guarantee that the ferret-passaged H5N1 virus would not be lethal and transmissible in humans. However, the same could be said about many laboratory-modified viruses, none of which have attracted the attention of the NSABB or the press. When we created the first animal virus from cloned DNA in 1981 (8), there were no calls to redact the paper or prevent further research, despite the theoretical possibility that this reagent might be used to produce more-virulent polioviruses. It was recognized that cloned viral DNA could be used to make important advances in our understanding of viral replication and pathogenesis.

Perhaps more troubling than the weak scientific basis for the NSABB's argument is the precedent set by withholding experimental details from a scientific publication. Science has always worked best when information is freely accessible. Unexpected individuals from diverse areas often solve difficult research problems. For decades, scientists have carried out experiments on pathogens, and the results have been published in a way that allows other scientists to repeat the experiments, verify conclusions, and expand on what is known. This cycle of publication, replication, and advancement has lead to most scientific and medical advances of the past century and has saved millions of lives. To suggest that studies of legitimate scientific merit should be published without complete methods and data is to abandon a system that brought us to the modern age of medicine.

The decision by the NSABB to restrict publication of data on H5N1 influenza viruses that are transmissible among ferrets is not rooted in sound scientific principles. Of greater concern is that it risks setting a precedent that will make it easier in the future to put in place highly restrictive regulations on scientific research and publication. Fear has clouded the NSABB's vision. We cannot allow fear to limit our ability to address medical problems.

REFERENCES

1. **Enserink M.** 2011. Infectious diseases. Controversial studies give a deadly flu virus wings. Science **334**:1192–1193.
2. **McNeil DG, Jr., Grady D.** 2 January 2012. How hard would it be for avian flu to spread? New York Times, New York, NY. http://www.nytimes.com/2012/01/03/health/an-explanation-of-how-avian-flu-spreads.html?pagewanted=all.
3. **Khuntirat BP, et al.** 2011. Evidence for subclinical avian influenza virus infections among rural Thai villagers. Clin. Infect. Dis. **53**:e107–e116.
4. **O'Donnell CD, Subbarao K.** 2011. The contribution of animal models to the understanding of the host range and virulence of influenza A viruses. Microbes Infect. **13**:502–515.
5. **Itoh Y, et al.** 2009. *In vitro* and *in vivo* characterization of new swine-origin H1N1 influenza viruses. Nature **460**:1021–1025.
6. **Sabin AB, Hennessen WA, Winsser J.** 1954. Studies on variants of poliomyelitis virus: I. Experimental segregation and properties of avirulent variants of three immunologic types. J. Exp. Med. **9**:551–576.
7. **Theiler M.** 1930. Susceptibility of white mice to the virus of yellow fever. Science **71**:367.
8. **Racaniello VR, Baltimore D.** 1981. Cloned poliovirus complementary DNA is infectious in mammalian cells. Science **214**:916–919.

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